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A CMOS Based Polysilicon Nanowire Biosensor Platform for Different Biological Targets

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Abstract

In this work, we demonstrate a promising polysilicon nanowire (poly-Si NW) biosensor platform. Several biomarkers, such as N-terminal prohormone brain natriuretic peptide (NT-proBNP), Low-density lipoprotein (LDL), Hemoglobin (Hb), and Hemoglobin A1C (HbA1c), for heart disease and diabetes are experimentally examined by the developed platform. Based on experimental results, the sensor responses of each biomarker is suitable for clinical diagnoses. Compared with conventional examination methods, using polysilicon nanowire biosensor not only reduce the inspection time but also economize the cost of diagnoses. Moreover, these implemented biosensor platform are made by a standard complementary metal-oxide-semiconductor (CMOS) process. Based on this technology, the developed devices can be easily integrated with different functional modules, such wireless and microfluidic systems. Therefore, this work demonstrates a good potential of CMOS based biosensor platform to accomplish the need of early diagnosis and point-of-care testing (POCT) system.

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Keywords: Nanowire; Biosensor; Point-of-care Testing; Clinical diagnosis; Biomarker

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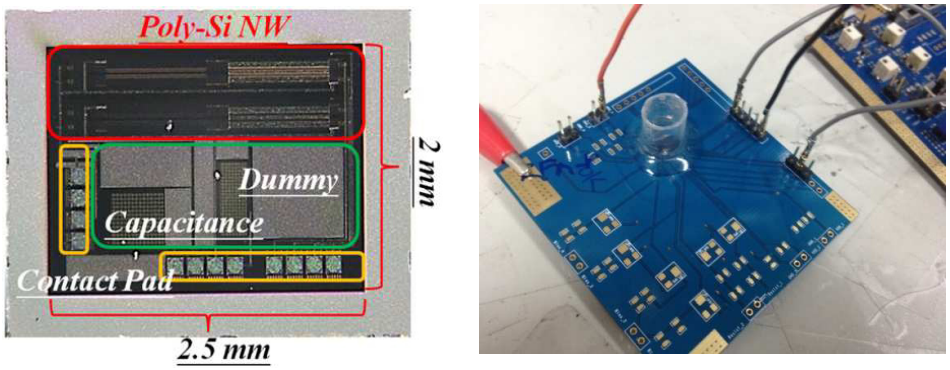
1. Introduction

As technologies and medical standards are continuously improved, many developed countries mortality declines. The average life expectancy of human beings has been increased and entered it is inevitable to enter an aging society. Human beings are threatened by several civilized illness, such as heart disease and diabetes. Therefore, health care at home becomes an important issue when people pay more and more attention to their health. So far, people used to use medical testing equipment in the medical institutions. However, there are still some of the inherent limitations, such as: bulky and complex operation, expensive, long detection time. Most important of all, people are required to go to the hospital to check the status of their body. In order to improve the examination efficiency of sensors, it is imperative to accomplish some needs: can be used at home, cheaper price, simple operation and higher accuracy.[1].

To address these requirements, a large number of solid state sensors, e.g. ion-sensitive field-effect-transistors [2-4], extended-gate field-effect transistors [5], microcantilevers [6, 7] and nanowires [8-10] have been developed in recent years. Considering of high sensitivity and fast response in these sensor devices, the nanowire biosensing technique is a promising candidate. Therefore, in this study, a poly-Si NW based biosensor chip was designed and fabricated by a CMOS process. After post-etching process and bonded to printed-circuit-board, two of four poly-Si NWs were exposed and introduced a conventional surface functionalized processes in order to immobilize the antibody of biological indicators we want to measure. All of biomarkers can successfully be monitored in clinical diagnoses level. Moreover, based on our previous work [11], the need of early diagnosis and point-of-care testing (POCT) system can be achieved.

2. Experimental Process

For the experiment, all chemical materials were bought from Sigma, including phosphate buffered saline (PBS), (3-aminopropyl) triethoxysilane (APTES), glutaraldehyde (GA) and bovine serum albumin (BSA). Antibody and protein pairs of LDL, Hb and HbA1c were purchased from Abcam. Anti NT-proBNP and NT-proBNP were acquired from Life Science Inc. To accomplish the purpose of low-cost and mass production, poly-Si NW biosensors were manufactured by a 0.35 μm 2P4M commercially-available CMOS fabrication technology, as shown in Fig. 1. (a).



(a) (b)

Fig. 1. (a) Picture of Poly-Si NW biosensor chip. Poly-Si NWs on right hand side were exposed to immobilize antibody. (b) Picture of measurement setup. Poly-Si NW biosensor chip was bond on printed-circuit-board and connected to a chopper differential-difference amplifier to get the amplified differential voltage signal [11].

In order to functionalize poly-Si NW biosensors, dry and wet etching process were introduced. After that, a conventional surface modification method was used. 2% APTES ethanol solution and 2.5% GA solution were

continuously applied on poly-Si NW to form the function group for 1 hour. Last, antibodies were immobilized. Before measurement, BSA was applied to block the unbinding site of antibodies.

The measurement setup is shown in Fig. 1 (b). The measurement procedure can be briefly described as follows: (a) Inject phosphate buffered saline (PBS) buffer solution for 5 minutes to obtain a reference base line; (b) Inject and incubate a specific concentration of testing target biomarker for 8 minutes; (c) remove unbinding biomarkers by PBS buffer; (d) measure the output voltage with PBS buffer.

3. Measurement results

NT-proBNP levels in the blood are used for screening, diagnosis of acute congestive heart failure. In addition, higher levels of LDL particles are associated with health problems, including cardiovascular disease. Furthermore, the ratio of HbA1c to Hb is an index of diabetes diagnosis. The higher ratio of HbA1c to Hb indicates the higher risks of developing complications related to diabetes. The normal range of Hb is 13.5 to 17.5 g/dl (135 to 175 mg/ml) for men, 12.0 to 15.5 g/dl (125 to 155 mg/ml) for women. And the normal range of HbA1c in plasma is about 4% to 5.6% of Hb concentration. In this work, the detection range of all biomarkers was designed for clinical diagnoses. The responses of different biomarkers can be shown in Fig. 2. As the figure shown, with different biomarkers, the output responses increased with higher biomarker concentration. The demarcation in clinical diagnoses of NT-proBNP and LDL are 463 pM and 700 μg/ml. On other hand, on Hb and HbA1c detection, the samples need to be diluted 10,000 times in order to avoid signal saturation. The clinical diagnoses level after 10,000 times diluted of Hb and HbA1c are 10 μg/ml and 71 nM.

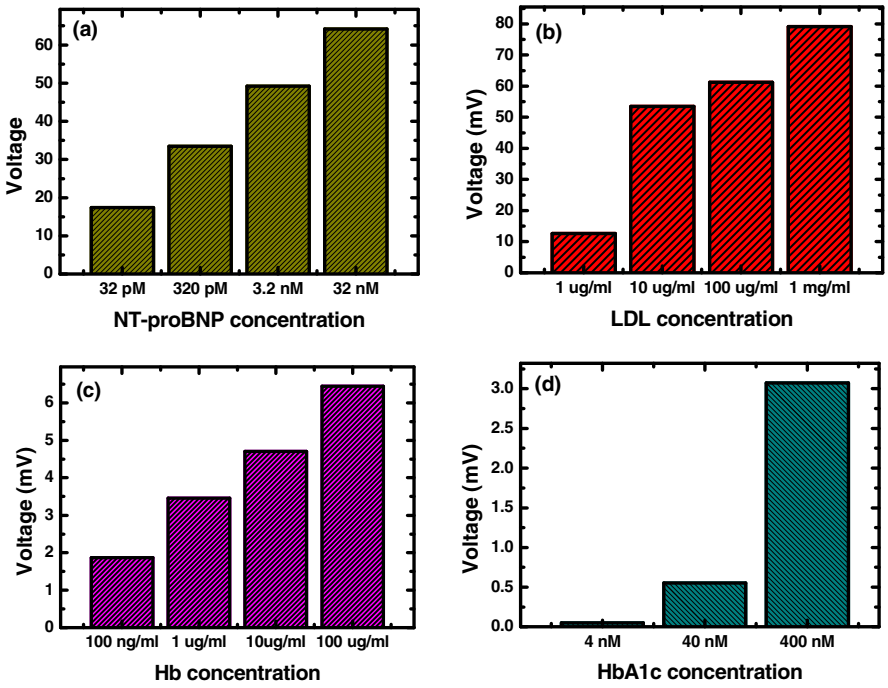


Fig. 2. The experimental results response of (a) NT-proBNP (b) LDL (c) Hb (d) HbA1C detection .

Detail experiment parameters are also shown in Table 1. The different outcomes between different proteins are caused by the different target concentrations, binding efficiency and isoelectric point value issue [12, 13]. Because the isoelectric point values of Hb and HbA1C are close to PBS pH value, we regulated the pH value of the PBS to pH 8 in order to enhance the signal responses. Based on this work, it is promising to employ the developed CMOS based poly-Si NW biosensor platform for POCT system.

Table 1 Detail experiment parameters of four biological indicators, NT-proBNP, LDL, Hb and HbA1c, in this research. The detection range of all biomarkers was designed for clinical diagnoses.

Biological Markers	Detection Range	Isoelectric Point Value	Measurement Buffer pH Value	Clinical Diagnoses level
NT-proBNP	32 pM ~ 32 nM	9.9	7.4	463 pM
LDL	1 μg/ml ~ 1 mg/ml	5.4	7.4	700 μg/ml
Hb	100 ng/ml ~ 100 μg/ml	6.852	8.0	10 μg/ml
HbA1c	4 nM ~400 nM	6.75	8.0	71 nM

4. Conclusion

In this paper, a poly-Si NW biosensor is successfully realized in a 0.35 μm 2P4M commercially-available CMOS process. The experimental results show that the biosensor chip can successfully detect the concentration difference in clinical diagnoses level. Consequently, with the advantages of label-free detection, high sensitivity, small size, low cost and CMOS compatibility, this poly-Si NW biosensor is applicable for rapid point-of-care testing (POCT) and clinical applications.

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